REMARKS

This Reply, filed in response to the Office Action mailed November 21, 2008, is believed to address all and every issue raised in the Action. A favorable reconsideration of the application is respectfully requested.

Claim Amendment and Status

Upon entry of the amendment, which is respectfully requested, claims 1-19 will be pending in the application, of which clams 1-12 are withdrawn from consideration as being directed to non-elected invention. Claim 14 is amended to cancel "or a hydrate thereof." Such amendment is made without disclaimer or prejudice. Claim 19 is newly added. Support for new claim 19 can be found in the specification at pages 15-20, and claims 14-18. No new matter is added and entry of the amendment is respectfully requested.

Formal Matters

Applicants thank the Examiner for considering the references submitted in IDS on September 27, 2004 and January 10, 2005 and returning initialed copies of the SB 08 forms.

Additionally, Applicants thank the Examiner for acknowledging the election without traverse of Group IV claims 13-16 and the elected compound "7-acetyl-5-(4-aminophenyl)-8(R)-methyl-8,9-dihydro-7H-1,3-dioxolo [4,5-h] [2,3]benzodiazepine" (Talampanel) in the reply filed on August 1, 2008. However, Applicants submit that in the Preliminary Amendment filed along with the Response to Restriction Election filed August 1, 2008, claims 17 and 18 were added and Applicants submitted that these claims fall within the elected Group IV and the elected species reads on claims 13 and 18. Claims 17 and 18, each depend from claim 13, and further limit the

compound defined in claim 13. Applicants respectfully request the Examiner consider claims 17 and 18, as well as currently added new claim 19, which depends from claim 13.

Response to Claim Rejections under 35 U.S.C. § 112, first paragraph

On page 2 of the Office Action, claims 13-16 are rejected under 35 U.S.C. 112, first paragraph, as allegedly failing to comply with the written description requirement. The Examiner alleges that the claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The Examiner asserts that specifically, the specification discloses only a limited number of species at page 14, lines [19-25], and these are not viewed as being reasonably representative of the genus in its claimed scope because no readily apparent combination of identifying characteristics is provided, other than the disclosure of those specific species as examples of the claimed genus.

On page 5 of the Office Action claims 13-16 are rejected under 35 U.S.C. 112, first paragraph, allegedly because the specification, while being enabling for "7-acetyl-5-(4-aminophenyl)-8(R)-methyl-8,9dihydro-7H-1,3-dioxolo [4,5-h] [2,3]benzodiazepine (Talampanel) in treating glioblastoma, does not reasonably provide enablement for each and every compound claimed. The Examiner's position is that the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the claimed invention commensurate in scope with these claims.

The Examiner states that the invention relates to a method of treating glioblastoma comprising administering a therapeutically effective amount of a compound having an activity of inhibiting an α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) receptor to a

patient with the disease. The Examiner alleges that the claims do not recite specific amount of compound or specific compound which inhibits AMPA receptor to a patient.

Applicants respectfully traverse.

Applicants note that the Office indicates that the specification, while being enabling for "7-acetyl-5-(4-aminophenyl)-8(R)-methyl-8,9dihydro-7H-1,3-dioxolo [4,5-h] [2,3]benzodiazepine (Talampanel) in treating glioblastoma, does not reasonably provide enablement for each and every compound claimed. The Office further indicates that the above compound is enabled by working examples. It appears that the Office intended to say that the specification is enabling for 2,3-dihydroxy-6-nitro-7-sulfamoyl-benzo(F)-quinoxaline (NBQX, claim 15) and [7-(1H-imidazol-1-yl)-6-nitro-2,3-dioxo-3,4-dihydroquinoxalin-1(2H)-yl]acetic acid (Compound A, claim 14), as used in the Examples.

The specification teaches the correlation between the activity of inhibiting AMPA receptor and treatment of glioblastoma

The specification teaches that the GluR1 and/or GluR4 subunits of the AMPA receptor was expressed widely in glioblastoma cells, particularly human primary glioblastoma cell and functioned as a Ca^{2+}-permeable AMPA receptor. Specifically, the disclosure states that the transformation of biological Ca^{2+}-permeable AMPA receptor into Ca^{2+}-non-permeable AMPA receptor by transfection of the GluR2(R) gene with adenovirus vector inhibited migration and induced the apoptosis of glioblastoma cells. In other words, the inhibition of Ca^{2+} permeability by the presence of the subunit GluR2(R) induces the cell death of glioblastoma cells. Further, the instant inventors found that in contrast, excess expression of Ca^{2+}-permeable AMPA receptor promoted not only the morphological change and growth of the tumor cell but also the migration ability. The specification discloses a method of testing the compound for treating glioblastoma.

Furthermore, it is disclosed that the compounds defined in the currently presented claims of the present application inhibit AMPA receptor activity. (See Specification pages 2-11).

The specification combined with knowledge in the art enables "a compound having an activity of inhibiting AMPA receptor" recited in claim 13

The specification provides a sufficient explanation and an extensive list of compounds which have an activity of inhibiting AMPA receptor. See pages 8, line 16 - page 11, line 13, and page 13, line 5 - page 20.

Also, methods of determining whether a compound has an AMPA receptor antagonist activity were known in the art before the filing date of the present application (e.g., WO 96/10023 and WO 97/17970).

Working Examples

The specification discloses methods of testing a compound for treating glioblastoma. The specification of the present application has working examples showing the glioblastoma treatment activity by quinoxalinedion type antagonist of AMPA receptor (e.g., compounds recited in claims 14 and 15). See Experimental Examples 1 and 2.

In order to show that structurally quite different AMPA receptor antagonists, e.g., pyridothiazine type (e.g., compound recited in claim 16) and benzodiazepine type (e.g., compounds recited in claims 17 and 18) antagonists of AMPA receptor exhibit gliolastoma treating activity, Applicants hereby submit an executed Rule 1.132 Declaration, in which pyridothiazine type (Test 1: compound B = 2-[N-(4-chlorophenyl)-N-methylamino]-4H-pyrido[3,2-e]-1,3-thiazin-4-one) and benzodiazepine type antagonists of AMPA receptor are tested (Tests 2 and 3: GYKI52466 HCl and Talampanel, respectively) and their results are

shown. As can be seen from the data presented in Rule 1.132 Declaration, pyridothiazine type and benzodiazepine type antagonists of AMPA receptor show activity of treating glioblastoma.

Therefore, since the specification and Rule 1.132 Declaration support the effects of five AMPA receptor antagonists which are structurally classified into three types, Applicants submit that the disclosure of the present application sufficiently describes the relationship between the activities of inhibiting AMPA receptor and of treating glioblastoma in a subject, without depending on a particular structure of a compound.

In particular, it would be clear to one skilled in the art that the compounds described in Tables on page 15-20 of the specification, which were known to have an activity of inhibiting an AMPA receptor, have an effect to treat glioblastoma, without undue experiment, because the specification discloses methods of testing a compound for treating glioblastoma. Furthermore, one skilled in the art would have been enabled, from the guidance provided in the specification combined with the knowledge and skill available in the art to make and use the full scope of the claimed subject matter.

Therapeutically effective amount

With regard to the recitation "a therapeutically effective amount," Applicants respectfully traverse the Examiner's rejection. The specification teaches that the dose is appropriately determined, depending on each case, in terms of the symptom, age, sex and the like of a subject to be treated. Additionally, the specification teaches that the daily dose of the compound of the present invention is about 100 to 2,000 mg per adult per day, and preferably about 900 mg per adult per day. Therefore, Applicants submit that the present claims are sufficiently enabled based on the knowledge and skill available in the art and the guidance provided in the specification. Applicants further assert that this recitation is definite in view of the general

descriptions in the specification relating to dosage and this recitation is generally acceptable under U.S. patent practice.

Accordingly, the rejection is not sustainable and withdrawal is respectfully requested.

Response to Claim Rejections under 35 U.S.C. § 112, second paragraph

On page 8, claims 13-16 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The Examiner's position is that claim 13 recites the limitation effective amount, however no effective amount have been listed in claims. The Examiner alleges that in the absence of specific amount or specific range of amounts, the claim would read on any amount (high or low), and requires Applicants to correct it.

Applicants respectfully traverse.

Again, as noted above, Applicants submit that the specification teaches that the dose is appropriately determined, depending on each case, in terms of the symptom, age, sex and the like of a subject to be treated. Additionally, the specification teaches that the daily dose of the compound of the present invention is about 100 to 2,000 mg per adult per day, and preferably about 900 mg per adult per day. Therefore, Applicants assert that the specification particularly points out and distinctly claims the subject matter of the invention and thus is not indefinite.

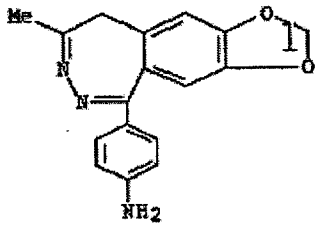
Accordingly, reconsideration and withdrawal of the rejection are respectfully requested.

Response to Rejections under 35 U.S.C. § 103(a)

On page 8 of the Office Action, claims 13-16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Paulsen et al. (WO 03/000928) in view of Andrasi et al. (USP 5,639,751) or vice versa.

The Examiner alleges that Paulsen teaches a cancer cell cell-surface molecule and cancer-specific promoter identification, targeting complexes, binding partners, and treatment methods. The Examiner indicates that Paulsen teaches the compound shown below:

RN 102771-26-6 HCAPLUS
CN Benzenamine, 4-(8-methyl-9H-1,3-dioxolo[4,5-h][2,3]benzodiazepin-5-yl)-
(CA INDEX NAME)



However, the Examiner concedes that the reference differs from the instant compound by acyl group.

The Examiner relies on Andrasi as teaching the claimed compound and the use of such compound in treating various diseases of central nervous system. The Examiner indicates that these compounds have been characterized as having a property of inhibiting AMPA receptors.

The Examiner alleges that it would have been obvious to one of ordinary skill in the art at the time of invention to substitute acyl group and come to the claimed invention. The Examiner further asserts that one would have been motivated because the reference teaches equivalency of the compound as disclosed by Paulsen with the claimed compound Talampanel. The Examiner believes that Andrasi also teaches that Talampanel is an AMPA receptor antagonist and Paulsen teaches similar compounds as discussed above in cancer treatment methods.

Applicants respectfully traverse.

Applicants respectfully submit that one skilled in the art would not have been motivated to combine Paulsen and Andrasi to reach the claimed subject matter with reasonable expectation of success.

Applicants note that Paulsen describes GRIA2 (AMPA2) as a cell surface molecule (see page 48, lines 22-27) of a target cancer to be treated, and the compounds of instant claims 15 and 17 as a binding partner of the GRIA2 (see page 100, lines 14-29), and further describes that glioblastoma is one of the target cancer (see page 130, lines 28-32). However, it is noted that the Office overlooked that the invention of Paulsen relates to a gene therapy of cancer and that a targeting complex of the binding partner and a bioreactive species has or provides an activity to treat cancer.

The concept of Paulsen's invention is shown in Fig. 1. Paulsen actually teaches the treatment of cancer using a bioreactive species such as DNA, and more specifically, by administering a DNA into a subject, a protein transcribed and duplicated from the DNA treats cancer. The cell surface molecule and the binding partner are used to selectively deliver the bioreactive species such as DNA to the target cancer cell. Thus, Paulsen fails to disclose or suggest that the binding partner itself (e.g., the compound recited in the claims) has an activity of treating cancer.

Andrasi is directed to treat various diseases of central nervous system. Andrasi teaches that the AMPA antagonist compound disclosed possesses valuable central nervous system effects, particularly muscle-relaxant, anticonvulsive and neuroprotective action and may be useful for the treatment of various central nervous system diseases. The Office fails to provide a rationale why one skilled in the art would have been motivated to combine teachings of

treatments of the central nervous system diseases area using a small molecule with a gene therapy of cancer area, with reasonable expectation or prediction of success.

Accordingly, even assuming that Paulsen could be combined with Andrasi, which they cannot, the present invention is not rendered obvious. Applicants respectfully request the reconsideration and withdrawal of the 35 U.S.C. § 103 rejection.

Conclusion

In view of the above, reconsideration and allowance of this application are now believed to be in order, and such actions are hereby solicited. If any points remain in issue which the Examiner feels may be best resolved through a personal or telephone interview, the Examiner is kindly requested to contact the undersigned at the telephone number listed below.

The USPTO is directed and authorized to charge all required fees, except for the Issue Fee and the Publication Fee, to Deposit Account No. 19-4880. Please also credit any overpayments to said Deposit Account.

Respectfully submitted,

/Sunhee Lee/

Sunhee Lee
Registration No. 53,892

SUGHRUE MION, PLLC
Telephone: (202) 293-7060
Facsimile: (202) 293-7860
WASHINGTON DC SUGHRUE/265550
65565
CUSTOMER NUMBER

Date: March 18, 2009